CONJUGATES OF ADENOSINE MIMETICS AND ARGININE-RICH PEPTIDES AS INHIBITORS AND FLUORESCENT PROBES FOR PROTEIN ARGININE METHYLTRANSFERASES

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The conjugates of an adenosine mimetic and oligo-L-arginine or oligo-D-arginine (ARCs) were initially designed as inhibitors and photoluminescent probes targeting basophilic protein kinases. Several ARCs and their fluorescent derivatives were investigated in biochemical assays with protein arginine methyltransferases (PRMTs), focusing particularly on PRMT1. PRMTs are a family of enzymes that catalyze the transfer of methyl group from *S*-adenosyl-$_L$-methionine (SAM) to arginine residues (Arg) in protein substrates, resulting in the formation of *S*-adenosyl-$_L$-homocysteine (SAH) and *N*-methylated Arg-comprising proteins. Although some PRMT-targeting biligand inhibitors have been reported previously,[1] our aim in this study was to assess if the compounds initially designed for targeting protein kinases could be "repurposed" for targeting PRMTs. A biochemical study was conducted with a panel of 23 ARCs, five ARC(Fluo) probes, and four ARC-Lum(Fluo) probes, which were screened against the recombinant PRMT1 in assay with detection of fluorescence anisotropy (FA) or time-gated luminescence intensity (TGLI).

Our study indicated that ARCs and arginine-rich peptides could serve as high-affinity ligands for PRMT1. We observed that ARC-1081 (a fluorescently labeled probe) could be displaced from its complex with PRM1 by SAM and SAH, showing that adenosine mimetic of ARCs binds to the SAM/SAH-binding site within PRMT1. All in all, the importance of this study was the finding that arginine-rich compounds could bind to PRMT1 – the predominant type I protein arginine methyltransferase in mammalian cells.

References

1. van Haren, M. J., Marechal, N., Troffer-Charlier, N., Cianciulli, A., Sbardella, G., Cavarelli, J., & Martin, N. I. (2017). Proceedings of the National Academy of Sciences. https://doi.org/10.1073/pnas.1618401114

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